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(54) Liquid preparation for external use

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(72) Inventor: Shigeki Suzuki
Terumo [phonetic] Corp., Ltd., 2-44-1 Hatagaya, Shibuya-ku, Tokyo-to

(71) Applicant: Terumo [phonetic] Corp., Ltd.
2-44-1 Hatagaya, Shibuya-ku, Tokyo-to

(74) Agent: Chiyoshi Takagi, Patent Attorney (1 other person)

1. Title of Invention: Liquid preparation for external use

2. Patent Claims

(1) A liquid preparation for external use, containing sulfur, a glycol, a carboxyvinyl polymer, a water-soluble alkaline substance in an amount at least sufficient for neutralizing the above carboxyvinyl polymer, and water.

(2) The above liquid preparation for external use described in Claim 1, characterized by the fact that it contains sulfur at 0.1-10 w/w %, a glycol at 1-80 w/w %, a carboxyvinyl polymer at 0.1-3 w/w %, a water-soluble alkaline substance in an amount sufficient for neutralizing the above carboxyvinyl polymer, and water for the balance, and that it has a pH of 4-8 and a viscosity of 1000-50,000 centipoise (20°C).

(3) The above liquid preparation for external use described in Claim 1 or 2, in which the glycol is propylene glycol, butylene glycol or polyethylene glycol.

(4) The above liquid preparation for external use described in Claim 1 or 2, in which the water-soluble alkaline substance is an alkylamine, dialkylamine, trialkylamine, alkanolamine, trialkylamine, alkanolamine, [repetition in the Japanese text] dialkanolamine, trialkanolamine, trimethylolaminomethane, ammonia or an alkali metal hydroxide, or a mixture of these compounds.

3. Detailed Description of the Invention

[Field in the Industry]

The present invention is related to a liquid preparation for external use. More specifically, it is related to a sulfur-containing liquid preparation for external dermatological use.

[Prior Art and Its Problems]

Sulfur has been used in lotions, ointments, etc. for the purposes of preventing and treating acne, and it has been used in many preparations for external dermatological use because of its bleaching, bactericidal and pesticidal effects. In traditional sulfur-containing preparations for external use, sulfur is treated with carboxymethylcellulose or methylcellulose and ethanol then dispersed in water.

However, in the traditional liquid preparations for external use, sulfur aggregates during production or storage and the aggregate facilitates its precipitation, causing deterioration of product quality. Accordingly, for sulfur-containing liquid preparations for external dermatological use, precipitation is considered to be inevitable, and the preparations are shaken before use to mix in the precipitated sulfur. However, even if the preparation is made homogeneous by shaking before use, precipitation occurs if use is not immediate. Thus, the use is complicated, and there are variations in the amount of the main component sulfur. Furthermore, many of the sulfur-containing liquid preparations for external dermatological use are for facial use for treating acne. When a sulfur-containing liquid preparation is used on the face, the sulfur remains as a white material after the solvent becomes dry. This is a problem with beautifying. In addition, the main component sulfur sheds off gradually as the solvent becomes dry. Thus, the drug used is not utilized sufficiently.

The inventors carried out active studies on this situation. As a result, they have achieved the invention that, when using a carboxyvinyl polymer, a water-soluble alkaline substance and a glycol in a sulfur-containing liquid preparation for external use, the sulfur does not aggregate or precipitate during storage and that after use there is no problem with beautifying with shedding of the drug.

[Means of Solving the Problems]

The present invention is related to a sulfur-containing liquid preparation for external dermatological use, containing sulfur, a glycol, a carboxyvinyl polymer, a water-soluble alkaline substance in an amount at least sufficient for neutralizing the above carboxyvinyl polymer, and water.

The present liquid preparation for external use preferably contains sulfur at 0.1-10 w/w %, a glycol at 1-80 w/w %, a carboxyvinyl polymer at 0.1-3 w/w %, a water-soluble alkaline substance in an amount sufficient for neutralizing the above carboxyvinyl polymer, and water for the balance, and has a pH of 4-8 and a viscosity of 1000-50,000 centipoise (20°C).

The carboxyvinyl polymer used in the present invention is a hydrophilic polymer obtained by polymerizing acrylic acid as a major component. For example, those commercially available products named Carbopol 934, Carbopol 940 and Carbopol 941 from Goodrich Chemical (USA), Highbiswako [phonetic] 103, Highbiswako 104, Highbiswako 105 from Wako

Pure Chemicals Corp., Ltd. can be used. The present liquid preparation for external use has a viscosity of 1000-50,000 centipoise, preferably 2000-7000 centipoise, at 20°C. In order to obtain the viscosity, the carboxyvinyl polymer is added at 0.1-3.0 wt% in the preparation. The carboxyvinyl polymer is generally used as a 1-5% aqueous solution. Preferably, after addition and stirring, water is added to adjust the concentration to the above range.

The carboxyvinyl polymer contains free carboxyl groups, and its aqueous solution is acidic. When the solution is neutralized with an alkali, it becomes a viscous gel. In the present invention the water-soluble alkaline substance for neutralizing the carboxyvinyl polymer is preferably, for example, an organic amine compound such as an alkylamine (e. g. methylamine, ethylamine, propylamine, etc.), dialkylamine (e. g. dimethylamine, diethylamine, dipropylamine, etc.), trialkylamine (e. g. trimethylamine, triethylamine, tripropylamine, etc.), alkanolamine (e. g. methanolamine, ethanolamine, propanolamine, etc.), dialkanolamine (e. g. dimethanolamine, diethanolamine, dipropanolamine, dibutanolamine, dibutanolamino acid, etc.), trialkanolamine (e. g. trimethanolamine, triethanolamine, tripropanolamine, tributanolamine, etc.), and trimethylolaminomethane. Besides, an aqueous solution of an inorganic alkali, such as ammonia or an alkali metal hydroxide can also be used.

The pH of the liquid preparation for external use is adjusted to a range, in which it does not irritate the skin and does not destroy the buffering action of the skin, preferably to pH 4-8. The water-soluble alkaline substance is added in an amount corresponding to the targeted pH of the liquid preparation for external use. In the present invention, as the carboxyvinyl polymer a neutralized carboxyvinyl polymer (such as Highbiswako-204, from Wako Pure Chemicals Corp., Ltd.) can also be used. In this case, there is no need to add the water-soluble alkaline substance. Although the amount added is 0, the pH of the liquid preparation for external use is controlled at 4-8.

For pulverizing the sulfur then homogeneously dispersing it in a water-containing solvent, the sulfur can be pulverized using a lower alcohol, such as ethyl alcohol, etc., or a ketone, such as acetone, methyl ethyl ketone, etc. However, these solvents are disadvantageous because they are irritating. The inventors carried out various studies, and, as a result, they found that glycols are highly suitable for the pulverization of sulfur. After the sulfur is pulverized in a glycol by sonication or homogenizer, a large amount of water is added to disperse sulfur without aggregation. The glycol and water mix homogeneously with each other, thereby obtaining a nice

sulfur dispersion. In a short period of time, the sulfur precipitates. Accordingly, the carboxyvinyl polymer is used. In this case, the glycol can be ethylene glycol, triethylene glycol, polyethylene glycol, propylene glycol, polypropylene glycol, 1,3-butylene glycol, etc. The glycol generally is contained at 1-80 wt% in the preparation.

The present liquid preparation for external use is a lotion preparation with the sulfur dispersed homogeneously. Unlike traditional sulfur-containing lotion preparations, it is not necessary to shake the preparation before use. When this liquid preparation is used on the skin, on the surface of the skin the water is evaporated, thereby forming a thin layer comprising the carboxylvinyl polymer and the glycol with sulfur particles immobilized on the surface of the skin by this thin layer. Accordingly, the major component, sulfur, is in contact with the diseased site over a long period of time, and an increase in sulfur utilization can be expected. Moreover, the glycol wets the sulfur. The glycol does not evaporate and even after a long period of time the beautifying effect remains excellent. In addition, there is no irritation since no lower alcohol or ketone is used.

Moreover, in the present liquid preparation for external use, various other substances can be used for the purposes of enhancing the action, etc. For example, phenol, resorcinol, resorcinol monoacetate, pyrogallol, benzoic acid, salicylic acid, mononitroguaiacol, tar preparation, selenium sulfide, cadmium sulfide, thiantol, thioxolone, ichthammol, adrenal cortical hormone, allantoin, sulfur preparation, antibiotic, bactericide, etc., can be used. It is preferable that those that do not interfere with the stability of the dispersion of sulfur be used.

With regard to production of the present liquid preparation for external use, first of all, sulfur is added to the glycol and mixed. Preferably, sulfur is added to the glycol, so that the amount of glycol is 3-10 times more. The mixing can be performed by sonication or in a homogenizer. The carboxyvinyl polymer, water-soluble alkaline substance and the remaining amount of water are added to the mixture of sulfur and glycol and stirred. The water-soluble alkaline substance can also be added as an aqueous solution. The sulfur is suspended homogeneously in the liquid preparation for external use.

In the following, practical examples are described, but the present invention is not to be limited to these examples.

Practical Examples 1-23

Sulfur, glycol, aqueous solution of carboxyvinyl polymer and purified water were prepared as shown in Table 1. The sulfur was added to the glycol, and mixed in a homogenizer. A 2 w/w % aqueous solution of the carboxyvinyl polymer and the remaining water were added and mixed homogeneously. The pH was adjusted as shown in Table 1 with triethanolamine, thereby obtaining a liquid preparation for external use.

Practical Example 24

Five g of sulfur was added to 20 g of 1,3-butanediol, and mixed in a homogenizer. Fifty g of 2 w/w % aqueous solution of the carboxyvinyl polymer, 1 mL of 30 w/w % ethanol solution of dl-camphor and 0.4 g of triethanolamine were added and mixed homogeneously. Then, 10 mL of 3 w/w % aqueous solution of homosulfamin was added, followed by addition of 15 mL of purified water, thereby obtaining a liquid preparation for external use.

Practical Example 25

Four g of sulfur was added to 20 g of 1,3-butanediol, and mixed in a homogenizer. Fifty g of a 1 w/w % aqueous solution of the carboxyvinyl polymer, 10 mL of 2 w/w % aqueous solution of allantoin, 1 mL of 15 w/w % ethanol solution of dl-camphor and 0.4 g of triethanolamine were added. Then, 15 mL of purified water was added and mixed homogeneously, thereby obtaining a liquid preparation for external use.

Practical Example 26

Six g of sulfur was added to 20 g of 1,3-butanediol, and mixed in a homogenizer. Fifty g of a 1 w/w % aqueous solution of the carboxyvinyl polymer, 2 g of resorcinol, 0.4 g of triethanolamine and 22 mL of purified water were added and mixed, thereby obtaining a liquid preparation for external use.

Test Example 1

Five grams of each of the compositions of Practical Examples 1-26 was filled into a sealed glass container with an inner diameter of 14 mm and a height of 100 mm, and, after 3 years of storage at 40°C, the stability of the composition was evaluated. The stability is the dispersion stability of sulfur powder, represented as the distance between the precipitation plane and liquid surface. The results are shown in Table 2, and thus it can be seen that almost all the compositions were stable.

For Practical Example 6, after 1 year of storage at 40°C a separation of 1 mm was formed between the precipitation plane and liquid surface. For Practical Example 10, since it was in a semisolid state, the concentration of the carboxyvinyl polymer was preferably 0.25-0.75 w/w %. For Practical Examples 11 and 12, after storage at 40°C for 1 and 6 months, respectively, a precipitation plane was formed, which was relatively unstable. Thus, it can be seen that the pH of the present liquid preparation for external use is particularly preferably 5-7.

For Practical Example 26, after storage at 40°C for 1 month, a separation of 60 mm was formed between the precipitation plane and liquid surface; thus, it was relatively unstable. The reason was considered to be that, by acidification due to the resorcinol, the pH decreased and consequently the viscosity of the liquid decreased.

Test Example 2

Each composition of Practical Examples 1-25 was subjected to sensory evaluation by a total of 50 healthy male and female adults, using the sulfur camphor lotion of the Japan Pharmacopoeia (11th edition) as control. Evaluation methods were, roughly speaking, touch and appearance during use of the present composition and the sulfur camphor lotion. The results of the overall evaluation of the contents are shown in Table 3. It can be seen from the results that for almost all of Practical Examples 1-25, the appearance during use was evaluated as very good. On the other hand, for the control, almost all the subjects evaluated it as "very concerned". For Practical Example 1 and Practical Example 5, the touch was not as good as for the others. The reason was considered to be related to the amount of the glycol. Thus, it can be said that the concentration of the glycol is more preferably 20 w/w % - 40 w/w %.

Test Example 3

Each composition of Practical Examples 1-25 was tested for facial adherence. In this test, 0.1 g of each composition from Practical Examples 1-25 and the sulfur camphor lotion of the Japan Pharmacopoeia (11th edition) as control, were spread in a range of about 25 cm^2 on the right and left sides of the face, respectively. After the application, the subject was allowed to move around freely for 3 hours and then the remaining sulfur was collected with a water-soaked gauze. The remaining amount of sulfur was measured, and the results are shown in Table 4. For almost all of the practical examples, the remaining rate of sulfur was high, except that Practical

Example 6 had a slightly lower rate. In contrast, the amount of sulfur remaining in the control was found to be very low.

Table 1. Composition of liquid preparations for external use

Component		Practical Example No.											
		1	2	3	4	5	6	7	8	9	10	11	12
sulfur		5	5	5	5	5	5	5	5	5	5	5	5
glycol	1,3-butane-diol	10	20	30	50	20	50	20	20	20	20	20	20
	polyethylene glycol 400												
	propylene glycol												
2 w/w % aqueous solution of carboxyvinyl polymer		25	25	25	25	25	5	12.5	25	37.5	50	25	25
pH		5	5	5	5	5	5	5	5	5	5	3	4

Component		Practical Example No.										
		13	14	15	16	17	18	19	20	21	22	23
sulfur		5	5	5	0.1	1	5	10	5	5	5	5
glycol	1,3-butane-diol	20	20	20	0.8	6	30	60				
	polyethylene glycol 400								20	20		
	propylene glycol										20	20
2 w/w % aqueous solution of carboxyvinyl polymer		25	25	25	25	25	25	25	25	25	25	25
pH		5	6	7	5	5	5	5	5	5	5	5

Table 2. Stability of liquid preparations for external use

Unit: mm

Practical Example No.	40°C, 75 % RH						room temperature					
	time						time					
	0	1 month	6 months	1 year	2 years	3 years	0	1 month	6 months	1 year	2 years	3 years
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	1	7	7	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	10	15	17	17	20	0	0	0	0	0	0
12	0	0	6	10	15	17	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0

Table 2. Stability of liquid preparations for external use (continued)

Unit: mm

Practical Example No.	40°C, 75% RH						room temperature					
	time						time					
	0	1 month	6 months	1 year	2 years	3 years	0	1 month	6 months	1 year	2 years	3 years
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	60	65	65	65	65	0	10	15	19	24	29

Table 3. Results of sensory test

Practical Example No.	sensation at application	sensation after application
1	O	Δ
2	O	O
3	O	O
4	O	O
5	O	Δ
6	O	O
7	O	O
8	O	O
9	O	O
10	O	O
11	O	O
12	O	O
13	O	O
14	O	O

O: good sensation

Δ: not a major concern, though the sensation was not very good

Table 3. Results of sensory test (continued)

Practical Example No.	sensation at application	sensation after application
15	O	O
16	O	O
17	O	O
18	O	O
19	O	O
20	O	O
21	O	O
22	O	O
23	O	O
24	O	O
25	O	O
26	O	O
control	Δ	X

O: good sensation

Δ: not a major concern though the sensation was not very good

X: a concern, with bad sensation

Table 4. Adherence rate

Practical Example No.	Adherence rate (%)
1	90
2	94
3	95
4	90
5	91
6	65
7	87
8	93
9	91
10	99
11	89
12	85
13	92
14	91
15	87
16	94
17	93
18	91

Table 4. Adherence rate (continued)

Practical Example No.	Adherence rate (%)
19	90
20	84
21	87
22	98
23	87
24	88
25	95
26	90
control	84

[Effects of the Invention]

The present liquid preparation for external use comprises sulfur, a glycol, a carboxyvinyl polymer and water. It is a dermatological preparation for external use, particularly suitable for prevention and treatment of acne. In the present liquid preparation for external use, the dispersion of sulfur is very good. Unlike traditional liquid preparations for external use, even over a long period of time, the sulfur does not precipitate. Moreover, after application of the

present liquid preparation for external use on the skin, sulfur does not whiten or shed off. Thus, applied sulfur is utilized efficiently.

In addition, since the present liquid preparation for external use is a lotion, unlike an ointment, it is not sticky on the skin. It can be easily removed by washing with water.

Applicant: Terumo [phonetic] Corp., Ltd.
Agent: Chiyoshi Takagi, Patent Attorney (1 other person)